

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number : 074846**

**Trade Name : ETODOLAC TABLETS 400MG**

**Generic Name: Etodolac Tablets 400mg**

**Sponsor : Invamed Inc.**

**Approval Date:February 28, 1997**

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION**      **074846**

## **CONTENTS**

	<b>Included</b>	<b>Pending Completion</b>	<b>Not Prepared</b>	<b>Not Required</b>
<b>Approval Letter</b>	<b>X</b>			
<b>Tentative Approval Letter</b>				
<b>Approvable Letter</b>				
<b>Final Printed Labeling</b>	<b>X</b>			
<b>Medical Review(s)</b>				
<b>Chemistry Review(s)</b>	<b>X</b>			
<b>EA/FONSI</b>				
<b>Pharmacology Review(s)</b>				
<b>Statistical Review(s)</b>				
<b>Microbiology Review(s)</b>				
<b>Clinical Pharmacology</b>				
<b>Biopharmaceutics Review(s)</b>				
<b>Bioequivalence Review(s)</b>	<b>X</b>			
<b>Administrative Document(s)</b>				
<b>Correspondence</b>				

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number      074846**

**APPROVAL LETTER**

ANDA 74-846

Invamed Inc.  
Attention: Mahendra Patel, Ph.D.  
2400 Route 130 North  
Dayton, NJ 08810

FEB 28 1997

|||||

Dear Sir:

This is in reference to your abbreviated new drug application dated February 1, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etodolac Tablets, 400 mg.

Reference is also made to your amendments dated August 6, 1996, and February 8, 14, 18, 24, 25, and 28, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etodolac Tablets, 400 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lodine® Tablets, 400 mg of Wyeth Ayerst Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Roger L. Williams, M.D.  
Deputy Center Director for  
Pharmaceutical Science  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER**      **074846**

**FINAL PRINTED LABELING**

ETODOLAC TABLETS, 400 mg

ANDA # 74-846

MAJOR AMENDMENT

(RESPONSE TO FDA LETTER DATED 07/22/96)

NDC 52189-350-24

**invamed inc.**

**Etodolac  
Tablets**

**400 mg**

CAUTION: Federal law prohibits  
dispensing without prescription.

**100 TABLETS**

**EACH TABLET CONTAINS:**

Etodolac ..... 400 mg

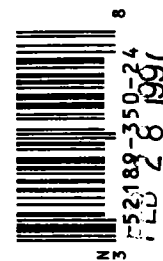
**USUAL DOSAGE:** See accompanying  
prescribing information for complete  
details.

Keep this and all drugs out of the reach  
of children.

Dispense in a well-closed container with  
a child-resistant closure.

Store at controlled room temperature  
15° to 30°C (59° to 86°F).

Manufactured By:  
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:  
Exp. Date:  
MF # 884

FEB 28 1997

NDC 52189-350-24

**invamed inc.**

**Etodolac  
Tablets**

**400 mg**

CAUTION: Federal law prohibits  
dispensing without prescription.

**100 TABLETS**

**EACH TABLET CONTAINS:**

Etodolac ..... 400 mg

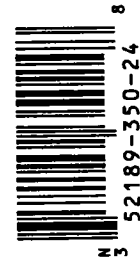
**USUAL DOSAGE:** See accompanying  
prescribing information for complete  
details.

Keep this and all drugs out of the reach  
of children.

Dispense in a well-closed container with  
a child-resistant closure.

Store at controlled room temperature  
15° to 30°C (59° to 86°F).

Manufactured By:  
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:  
Exp. Date:  
MF # 884

NDC 52189-350-24

**invamed inc.**

**Etodolac  
Tablets**

**400 mg**

CAUTION: Federal law prohibits  
dispensing without prescription.

**100 TABLETS**

**EACH TABLET CONTAINS:**

Etodolac ..... 400 mg

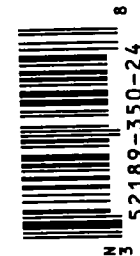
**USUAL DOSAGE:** See accompanying  
prescribing information for complete  
details.

Keep this and all drugs out of the reach  
of children.

Dispense in a well-closed container with  
a child-resistant closure.

Store at controlled room temperature  
15° to 30°C (59° to 86°F).

Manufactured By:  
INVAMED INC., Dayton, NJ 08810 USA



Lot No.:  
Exp. Date:  
MF # 884

FEB 28 1997

000049

ETODOLAC TABLETS, 400 mg  
ANDA # 74-846

MAJOR AMENDMENT

(RESPONSE TO FDA LETTER DATED 07/22/96)

NDC 52189-350-29

**invamed inc.**

---

**Etodolac  
Tablets**

**400 mg**

CAUTION: Federal law prohibits  
dispensing without prescription.

---

**500 TABLETS**

**EACH TABLET CONTAINS:**

Etodolac ..... 400 mg

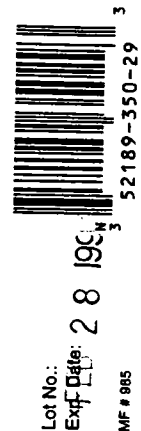
**USUAL DOSAGE:** See accompanying  
prescribing information for complete  
details.

Keep this and all drugs out of the reach of  
children.

Dispense in a well-closed container with a  
child-resistant closure.

Store at controlled room temperature  
15° to 30°C (59° to 86°F).

Manufactured By:  
INVAMED INC., Dayton, NJ 08810 USA



NDC 52189-350-29

**invamed inc.**

---

**Etodolac  
Tablets**

**400 mg**

CAUTION: Federal law prohibits  
dispensing without prescription.

---

**500 TABLETS**

**EACH TABLET CONTAINS:**

Etodolac ..... 400 mg

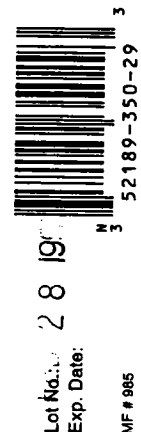
**USUAL DOSAGE:** See accompanying  
prescribing information for complete  
details.

Keep this and all drugs out of the reach of  
children.

Dispense in a well-closed container with a  
child-resistant closure.

Store at controlled room temperature  
15° to 30°C (59° to 86°F).

Manufactured By:  
INVAMED INC., Dayton, NJ 08810 USA



NDC 52189-350-29

**invamed inc.**

---

**Etodolac  
Tablets**

**400 mg**

CAUTION: Federal law prohibits  
dispensing without prescription.

---

**500 TABLETS**

**EACH TABLET CONTAINS:**

Etodolac ..... 400 mg

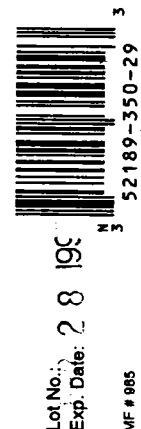
**USUAL DOSAGE:** See accompanying  
prescribing information for complete  
details.

Keep this and all drugs out of the reach of  
children.

Dispense in a well-closed container with a  
child-resistant closure.

Store at controlled room temperature  
15° to 30°C (59° to 86°F).

Manufactured By:  
INVAMED INC., Dayton, NJ 08810 USA



000054

Marygo

ETODOLAC TABLETS, 400 mg

ANDA # 74-846

MAJOR AMENDMENT

(RESPONSE TO FDA LETTER DATED 07/22/96)

NDC 52189-350-30

**invamed inc.**

**Etodolac  
Tablets**

**400 mg**

CAUTION: Federal law prohibits  
dispensing without prescription.

**1000 TABLETS**

**EACH TABLET CONTAINS:**

Etodolac ..... 400 mg

**USUAL DOSAGE:** See accompanying  
prescribing information for complete  
details.

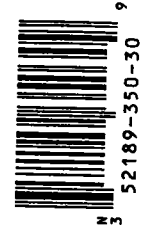
Keep this and all drugs out of the reach of  
children.

Dispense in a well-closed container with a  
child-resistant closure.

Store at controlled room temperature  
15° to 30°C (59° to 86°F).

Manufactured By:

**INVAMED INC., Dayton, NJ 08810 USA**



Lot No.: 281997  
Exp. Date:

MF # 986

NDC 52189-350-30

**invamed inc.**

**Etodolac  
Tablets**

**400 mg**

CAUTION: Federal law prohibits  
dispensing without prescription.

**1000 TABLETS**

**EACH TABLET CONTAINS:**

Etodolac ..... 400 mg

**USUAL DOSAGE:** See accompanying  
prescribing information for complete  
details.

Keep this and all drugs out of the reach of  
children.

Dispense in a well-closed container with a  
child-resistant closure.

Store at controlled room temperature  
15° to 30°C (59° to 86°F).

Manufactured By:

**INVAMED INC., Dayton, NJ 08810 USA**



Lot No.: 281997  
Exp. Date:

MF # 986

NDC 52189-350-30

**invamed inc.**

**Etodolac  
Tablets**

**400 mg**

CAUTION: Federal law prohibits  
dispensing without prescription.

**1000 TABLETS**

**EACH TABLET CONTAINS:**

Etodolac ..... 400 mg

**USUAL DOSAGE:** See accompanying  
prescribing information for complete  
details.

Keep this and all drugs out of the reach of  
children.

Dispense in a well-closed container with a  
child-resistant closure.

Store at controlled room temperature  
15° to 30°C (59° to 86°F).

Manufactured By:

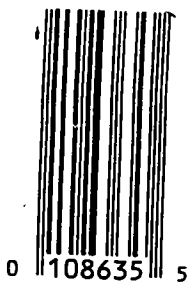
**INVAMED INC., Dayton, NJ 08810 USA**



Lot No.: 281997  
Exp. Date:

MF # 986

000059



## ETODOLAC TABLETS

**Description:**  
Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not known but is believed to be associated with the inhibition of prostaglandin biosynthesis. Etodolac is a racemic mixture of (-)-R- and (+)-S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the (+)-S-form is biologically active. Both enantiomers are stable and there is no (-)-R to (+)-S conversion in vivo.



The molecular formula for etodolac is  $C_{17}H_{21}NO_3$ . The molecular weight of the base is 287.37. It has a pKa of 4.65 and an n-octanol:water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

Each tablet, for oral administration, contains 400 mg of etodolac. In addition, each tablet contains the following inactive ingredients: D&C Yellow No. 10 aluminum lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, sodium starch glycolate, synthetic yellow iron oxide and titanium dioxide.

### Clinical Pharmacology

#### PHARMACOLOGY

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not known but is believed to be associated with the inhibition of prostaglandin biosynthesis.

Etodolac is a racemic mixture of (-)-R- and (+)-S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the (+)-S-form is biologically active. Both enantiomers are stable and there is no (-)-R to (+)-S conversion in vivo.

#### PHARMACODYNAMICS

Analgesia was demonstrable 1/2 hour following single doses of 200 to 400 mg etodolac, with the peak effect occurring in 1 to 2 hours. The analgesic effect generally lasted for 4 to 6 hours (see Clinical Trials).

#### PHARMACOKINETICS

The pharmacokinetics of etodolac have been evaluated in 267 normal subjects, 44 elderly patients (>65 years old), 19 patients with renal failure (creatinine clearance 37 to 66 mL/min), 9 patients on hemodialysis, and 10 patients with compensated hepatic cirrhosis.

Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption.

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, furosemide or hydrochlorothiazide.

#### ABSORPTION

Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg tablets were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from either the tablet or tablet formulation, is at least 80%. Etodolac does not undergo significant first-pass metabolism.

clearance 37 to 88 mL/min) creatinine on hemodialysis, and 10 patients with compensated hepatic cirrhosis.

Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption.

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, ferrous sulfate or hydrochlorothiazide.

#### ABSORPTION

Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg tablets were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from either the tablet or tablet formulation, is at least 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. Mean ( $\pm$  1 SD) peak plasma concentrations range from approximately  $14 \pm 4$  to  $37 \pm 9$  mcg/mL after 200 to 600 mg single doses and are reached in  $80 \pm 30$  minutes (see Table 1 for summary of pharmacokinetic parameters). The dose-proportionality based on AUC (the area under the plasma concentration-time curve) is linear following doses up to 600 mg every 12 hours. Peak concentrations are dose-proportional for both total and free etodolac following doses up to 400 mg every 12 hours, but following a 600 mg dose, the peak is about 20% higher than predicted on the basis of lower doses.

Table 1. Etodolac Study: Mean Pharmacokinetic Parameters

Etodolac Formulation	Mean $\pm$ SD
Etodolac (200 mg tablet)	$14 \pm 4$ mcg/mL
Etodolac (400 mg tablet)	$27 \pm 9$ mcg/mL
Etodolac (600 mg tablet)	$37 \pm 9$ mcg/mL
Etodolac (200 mg solution)	$14 \pm 4$ mcg/mL
Etodolac (400 mg solution)	$27 \pm 9$ mcg/mL
Etodolac (600 mg solution)	$37 \pm 9$ mcg/mL

#### Antacid Effects

The extent of absorption of etodolac is not affected when etodolac is administered with an antacid. Coadministration with an antacid decreases the peak concentration reached by about 15 to 20%, with no measurable effect on time-to-peak.

#### Food Effects

The extent of absorption of etodolac is not affected when etodolac is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one half and increases the time-to-peak concentration by 1.4 to 3.8 hours.

#### Distribution

Etodolac has an apparent steady-state volume of distribution about 0.362 L/kg. Within the therapeutic dose range, etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied.

#### Metabolism

Etodolac is extensively metabolized in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. The inter-subject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

#### Protein Binding

Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

#### Elimination

The mean plasma clearance of etodolac, following oral dosing is  $47 (\pm 16)$  mL/min, and terminal disposition half-life is  $7.3 (\pm 4.0)$  hours. Approximately 72% of the administered dose is recovered in the urine as the following, indicated as % of the administered dose:

- etodolac, unchanged 1%
- etodolac glucuronide 13%
- hydroxylated metabolites (6-, 7-, and 8-OH) 5%
- hydroxylated metabolite glucuronides 20%
- unidentified metabolites 33%

Fecal excretion accounted for 16% of the dose.

#### SPECIAL POPULATIONS

##### Elderly Patients

In clinical studies, etodolac clearance was reduced by about 15% in older patients ( $>65$  years of age). In these studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, on the basis of body size (see Precautions—GERIATRIC POPULATION), as they may be more sensitive to antiprostaglandin effects than younger patients (see Precautions—GERIATRIC POPULATION).

##### Renal Impairment

Studies in patients with mid-to-moderate

- etodolac, unchanged	1%
- etodolac glucuronide	13%
- hydroxylated metabolites (6-, 7-, and 8-OH)	5%
- hydroxylated metabolite glucuronides	20%
- unidentified metabolites	33%

Fecal excretion accounted for 16% of the dose.

#### SPECIAL POPULATIONS

##### Elderly Patients

In clinical studies, etodolac clearance was reduced by about 15% in older patients (>65 years of age). In these studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, on the basis of body size (see Precautions—GERIATRIC POPULATION), as they may be more sensitive to antiprostaglandin effects than younger patients (see Precautions—GERIATRIC POPULATION).

##### Renal Impairment

Studies in patients with mild-to-moderate renal impairment (creatinine clearance 37 to 88 mL/min) showed no significant differences in the disposition of total and free etodolac. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Nevertheless, etodolac is not dialyzable.

##### Hepatic Impairment

In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Although no dosage adjustment is generally required in this patient population, etodolac clearance is dependent on hepatic function and could be reduced in patients with severe hepatic failure.

##### Clinical Trials

##### ANALGESIA

Controlled clinical trials in analgesia were single-dose, randomized, double-blind, parallel studies in three pain models, including dental extractions. The analgesic effective dose for etodolac established in these acute pain models was 200 to 400 mg. The onset of analgesia occurred approximately 30 minutes after oral administration. 200 mg of etodolac provided efficacy comparable to that obtained with aspirin (650 mg). 400 mg of etodolac provided efficacy comparable to that obtained with acetaminophen with codeine (600 mg + 50 mg). The peak analgesic effect was between 1 to 2 hours. Duration of relief averaged 4 to 5 hours for 200 mg of etodolac and 5 to 6 hours for 400 mg of etodolac as measured by when approximately half of the patients required remedication.

##### OSTEOARTHRITIS

The use of etodolac in managing the signs and symptoms of osteoarthritis of the hip or knee was assessed in double-blind, randomized, controlled clinical trials in 341 patients. In patients with osteoarthritis of the knee, etodolac in doses of 600 to 1000 mg/day, was better than placebo in two studies. The clinical trials in osteoarthritis used b.i.d. dosage regimens.

##### Indications and Usage

Etodolac tablets are indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis. Etodolac tablets are also indicated for the management of pain.

##### Contraindications

Etodolac is contraindicated in patients with known hypersensitivity to etodolac. Etodolac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to etodolac have been reported in such patients (see Warnings—ANAPHYLACTOID REACTIONS).

##### Warnings

**RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) THERAPY.**

Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months' to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk

4

subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

#### ANAPHYLACTOID REACTIONS

Anaphylactoid reactions may occur in patients without prior exposure to etodolac. Etodolac should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, who exhibit severe, potentially fatal bronchospasm after taking aspirin or other nonsteroidal anti-inflammatory drugs. Fatal reactions have been reported in such patients (see **Contraindications and Precautions—Pre-existing Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

#### ADVANCED RENAL DISEASE

In cases with advanced kidney disease, as with other NSAIDs, treatment with etodolac should only be initiated with close monitoring of the patient's kidney function (see **Precautions—Renal Effects**).

#### PREGNANCY

In late pregnancy, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus (see **Precautions—Teratogenic Effects—Pregnancy Category C**).

#### Precautions

##### GENERAL PRECAUTIONS

##### Renal Effects

As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.

A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction; those taking diuretics; and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in **Adverse Reactions**) may be attributable to these metabolites should be considered.

##### Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including etodolac. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Meaningful elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with etodolac. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with etodolac. Rare cases of liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), etodolac should be discontinued.

##### Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs including etodolac. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including etodolac, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

##### Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs, including etodolac. Therefore, etodolac should be used with caution in patients with fluid retention, hypertension, or heart failure.

##### Pre-existing Asthma

About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive

5

or liver dysfunction; those taking diuretics; and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etidolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in Adverse Reactions) may be attributable to these metabolites should be considered.

#### **Hepatic Effects**

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including etidolac. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Mean- ingful elevations of ALT or AST (approx- imately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with etidolac. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be eval- uated for evidence of the development of a more severe hepatic reaction while on therapy with etidolac. Rare cases of liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), etidolac should be discontinued.

#### **Hematological Effects**

Anemia is sometimes seen in patients receiving NSAIDs including etidolac. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, includ- ing etidolac, should have their hemo- globin or hematocrit checked if they exhibit any signs or symptoms of anemia. All drugs which inhibit the biosynthe- sis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

#### **Fluid Retention and Edema**

Fluid retention and edema have been observed in some patients taking NSAIDs, including etidolac. Therefore, etidolac should be used with caution in patients with fluid retention, hyper- tension, or heart failure.

#### **Pre-existing Asthma**

About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sen- sitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin- sensitive patients, etidolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

#### **INFORMATION FOR PATIENTS**

Etidolac, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastroin- testinal bleeding, which may result in hospitalization and even fatal outcomes.

Physicians may wish to discuss with their patients the potential risks (see Warnings, Precautions, Adverse Reac- tions) and likely benefits of nonsteroidal anti-inflammatory drug treatment.

Patients on etidolac should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Because serious gastrointestinal tract ulcerations and bleeding can occur with- out warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcera-

tions and bleeding and should inform them of the importance of this follow-up (see Warnings—RISK OF GILCERATION, BLEEDING AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY THERAPY).

Patients should also be instructed to seek medical emergency help in case of an occurrence of anaphylactoid reactions (see Warnings).

#### LABORATORY TESTS

Patients on long-term treatment with etodolac, as with other NSAIDs, should have their hemoglobin or hematocrit checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash, etc.) and if abnormal liver tests are detected, persist or worsen, etodolac should be discontinued.

#### DRUG INTERACTIONS

##### Antacids

The concomitant administration of antacids has no apparent effect on the extent of absorption of etodolac. However, antacids can decrease the peak concentration reached by 15% to 20% but have no detectable effect on the time-to-peak.

##### Aspirin

When etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.

##### Warfarin

Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac should not require dosage adjustment of either drug. However, there have been a few spontaneous reports of prolonged prothrombin times in etodolac-treated patients receiving concomitant warfarin therapy. Caution should be exercised because interactions have been seen with other NSAIDs.

##### Cyclosporine, Digoxin, Lithium, Methotrexate

Etodolac, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of digoxin, lithium, and methotrexate and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.

##### Phenylbutazone

Phenylbutazone causes increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.

#### DRUG/LABORATORY TEST INTERACTIONS

The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose-relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.

#### CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 80 mg/m<sup>2</sup>, respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3.0 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 mcg/mL) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m<sup>2</sup>). However,

7

increase in the number of gaps (3.0 to 5.3% unstained regions in the chromatin without dislocation) among the etodolac-treated cultures (50 to 200 mcg/mL) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (34 mg/m<sup>2</sup>). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.

#### PREGNANCY

##### *Teratogenic Effects—Pregnancy Category C*

In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2 to 14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship.

There are no adequate or well-controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during late pregnancy should be avoided.

#### LABOR AND DELIVERY

In rat studies with etodolac, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of etodolac on labor and delivery in pregnant women are unknown.

#### NURSING MOTHERS

It is not known whether etodolac is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etodolac, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

#### PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

#### GERIATRIC POPULATION

As with any NSAID, however, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. In patients 65 years and older, no substantial differences in the side effect profile of etodolac were seen compared with the general population (see Clinical Pharmacology—PHARMACOKINETICS).

#### Adverse Reactions

Adverse-reaction information for etodolac was derived from 2,629 arthritic patients treated with etodolac in double-blind and open-label clinical trials of 4 to 320 weeks in duration and worldwide postmarketing surveillance studies. In clinical trials, most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials, because of adverse events, was up to 10% for patients treated with etodolac.

New patient complaints (with an incidence greater than or equal to 1%) are listed below by body system. The incidences were determined from clinical trials involving 465 patients with osteoarthritis treated with 300 to 500 mg of etodolac b.i.d. (i.e., 600 to 1000 mg/day).

#### INCIDENCE GREATER THAN OR EQUAL TO 1%—PROBABLY CAUSALLY RELATED:

Body as a whole—Chills and fever.

Digestive system—Dyspepsia (10%), abdominal pain\*, diarrhea\*, flatulence\*, nausea\*, constipation, gastritis, melena, vomiting.

Nervous system—Asthenia/malaise\*, dizziness\*, depression, nervousness.

Skin and appendages—Pruritus, rash.

Special senses—Blurred vision, tinnitus.

Urogenital system—Dysuria, urinary frequency.

\*Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient complaints occurring in fewer than 3%, but more than 1%, are unmarked.

#### INCIDENCE LESS THAN 1%—PROBABLY CAUSALLY RELATED (Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rare and are italicized)

Body as a whole—*Allergic reaction, anaphylactoid reaction.*

Cardiovascular system—Hypertension, congestive heart failure, flushing, palpitations, syncope, vasculitis (including necrotizing and allergic).

Digestive system—Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, cholestatic hepatitis, hepatitis, cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis, peptic ulcer with or without bleeding and/or perforation, intestinal ulceration, pancreatitis.

Hemic and lymphatic system—Ecchymosis, anemia, thrombocytopenia, bleeding time increased, agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.

Metabolic and nutritional—Edema, serum creatinine increase, hyperglycemia in previously controlled diabetic patients.

Special senses—Blurred vision, tinnitus.  
Urogenital system—Dysuria, urinary frequency.

Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient complaints occurring in fewer than 3%, but more than 1%, are unmarked.

**INCIDENCE LESS THAN 1%—PROBABLY CAUSALLY RELATED** (Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized)

Body as a whole—*Allergic reaction, anaphylactoid reaction.*

Cardiovascular system—Hypertension, congestive heart failure, flushing, palpitations, syncope, vasculitis (including necrotizing and allergic).

Digestive system—Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, cholestatic hepatitis, hepatitis, cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis, peptic ulcer with or without bleeding and/or perforation, intestinal ulceration, pancreatitis.

Hemic and lymphatic system—Ecchymosis, anemia, thrombocytopenia, bleeding time increased, agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.

Metabolic and nutritional—Edema, serum creatinine increase, hyperglycemia in previously controlled diabetic patients.

Nervous system—Insomnia, somnolence.  
Respiratory system—Asthma.

Skin and appendages—Angioedema, sweating, urticaria, vesiculobullous rash, cutaneous vasculitis with purpura, Stevens-Johnson syndrome, hyperpigmentation, erythema multiforme.

Special senses—Photophobia, transient visual disturbances.

Urogenital system—Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.

**INCIDENCE LESS THAN 1%—CAUSAL RELATIONSHIP UNKNOWN** (Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians).

Body as a whole—Infection, headache.

Cardiovascular system—Arrhythmias, myocardial infarction, cerebrovascular accident.

Digestive system—Esophagitis with or without stricture or cardiospasm, colitis.

Metabolic and nutritional—Change in weight.

Nervous system—Paresthesia, confusion.

Respiratory system—Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.

Skin and appendages—Alopecia, maculopapular rash, photosensitivity, skin peeling.

Special senses—Conjunctivitis, deafness, taste perversion.

Urogenital system—Cystitis, hematuria, leukorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities.

**Overdoseage**

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur and coma has occurred following massive ibuprofen or mefenamic-acid overdose. Hypertension, acute renal failure, and respiratory depression may occur but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, or hemodialysis, or hemoperfusion would probably not be useful due to etodolac's high protein binding.

#### **Dosage and Administration**

As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac, the dose and frequency should be adjusted to suit an individual patient's needs.

Dosage adjustment of etodolac is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function. (See Precautions—GENERAL PRECAUTIONS, Renal Effects).

#### **ANALGESIA**

The recommended total daily dose of etodolac for acute pain is up to 1000 mg, given as 200–400 mg every 6 to 8 hours. In some patients, if the potential benefits outweigh the risks, the dose may be increased to 1200 mg/day in order to achieve a therapeutic benefit that might not have been achieved with 1000 mg/day. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

#### **OSTEOARTHRITIS**

The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d. or 500 mg b.i.d.

may further decrease renal function in some patients with impaired renal function. (see Precautions—GENERAL PRECAUTIONS, Renal Effects).

#### ANALGESIA

The recommended total daily dose of etodolac for acute pain is up to 1000 mg, given as 200-400 mg every 6 to 8 hours. In some patients, if the potential benefits outweigh the risks, the dose may be increased to 1200 mg/day in order to achieve a therapeutic benefit that might not have been achieved with 1000 mg/day. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

#### OSTEOARTHRITIS

The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis is: 300 mg b.i.d., i.i.d., or 400 mg b.i.d., or 500 mg b.i.d. During long-term administration, the dose of etodolac may be adjusted up or down depending on the clinical response of the patient. A lower dose of 600 mg/day may suffice for long-term administration. In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose. Physicians should be aware that doses above 1000 mg/day may not have been adequately evaluated in well-controlled clinical trials.

In chronic conditions, a therapeutic response to therapy with etodolac is sometimes seen within one week of therapy, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

#### How Supplied

Etodolac Tablets 400 mg are oval shaped, yellow, film coated, unscored, engraved INV 350 on one side are supplied as follows:

#### Invamed Labels

NDC 52189-350-24 in bottles of 100 tablets

NDC 52189-350-29 in bottles of 500 tablets

NDC 52189-350-30 in bottles of 1000 tablets

#### Apothecan-Invamed Distributor Labels

NDC 62269-350-24 in bottles of 100 tablets

NDC 62269-350-29 in bottles of 500 tablets

NDC 62269-350-30 in bottles of 1000 tablets

#### Storage

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Dispense in a light-resistant container.

#### Caution

Federal law prohibits dispensing without prescription.

Manufactured by:  
INVAMED, INC.  
Dayton, NJ 08810 USA

Date of Revision: February 1997  
L-1086; MF# 9838

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER     074846**

**CHEMISTRY REVIEW(S)**

1. CHEMISTRY REVIEW NO. 3
2. ANDA # 74-846
3. NAME AND ADDRESS OF APPLICANT  
Invamed Inc.  
Attention: Mahendra Patel, Ph.D.  
2400 Rt 130 North  
Dayton, NJ 08810
4. LEGAL BASIS FOR SUBMISSION  
Based on Wyeth-Ayerst Lab's Lodine Tab, 400 mg  
Patent #4076831 expires on 2/28/97.
5. SUPPLEMENT(s) N/A      6. PROPRIETARY NAME N/A
7. NONPROPRIETARY NAME Etodolac Tablets
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:  
FDA: 2/7/97      Deficiency faxed to firm.  
  
Firm: 2/1/96      Orig. ANDA submitted.  
      2/8/97      Response to fax letter of 2/7/97.  
      2/14/97     Tel.amendment  
      2/18/97     Tel.amendment  
      2/24/97     Tel.amendment  
      2/25/97     Tel.amendment
10. PHARMACOLOGICAL CATEGORY      11. Rx or OTC  
Anti-inflammatory                      Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM                      14. POTENCY  
Tablets                                      400 mg
18. CONCLUSIONS AND RECOMMENDATIONS  
Approval
19. REVIEWER:                      DATE COMPLETED:  
J. Fan                                      2/12/97  
  2/26/97 (Revised)

cc: ANDA 74-846  
DUP File  
Division File

Endorsements:

HFD-623/J.Fan/2/26/97  
HFD-623/V.Sayeed, Ph.D./2/26/97  
x:\new\firmam\invamed\ltrs&rev\74846n3.d  
F/T by: gp/2/27/97

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER 074846**

**BIOEQUIVALENCE REVIEWS**

9.3  
ANDA 74-846

Invamed Inc.  
Attention: Mahendra Patel, Ph.D.  
2400 Route 130 North  
Dayton NJ 08810  
|||||

JUL 31 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Etodolac Tablets 400 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.5 at 37°C using USP 23 Apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

Not less than            of the labeled amount of etodolac in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/ Keith K. Chan, Ph.D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

D W

JUL 29 1996

Etodolac  
Tablet, 400 mg  
ANDA # 74-846  
Reviewer: S.P. Shrivastava  
WP #74846sdw.296

Invamed, Inc.  
Dayton, NJ  
Submission Date:  
February 1, 1996

## Review of Two Bioequivalence Studies, and Dissolution Data

### I. Introduction

Etodolac is a pyranocarboxylic acid chemically designated as ( $\pm$ ) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. It is a nonsteroidal anti-inflammatory drug with anti-inflammatory, analgesic, and antipyretic properties. The drug is a racemic mixture of R- and S-etodolac, the S-form being biologically active. Both enantiomers are stable and there is no R to S conversion *in vivo*.

Etodolac is well absorbed with a relative bioavailability of 100% when 200 mg capsules were compared with a solution. The systemic availability is at least 80% and etodolac does not undergo significant first-pass metabolism following oral administration. When administered orally, etodolac exhibits characteristics which are well described by a two-compartment model with first-order absorption. Mean ( $\pm$  SD) peak plasma concentrations range from approximately  $14 \pm 4$  to  $37 \pm 9$   $\mu\text{g/mL}$  after 200 to 600 mg single doses and are reached in  $80 \pm 30$  minutes. The mean plasma clearance of etodolac is  $47 (\pm 16)$  mL/h/kg, and terminal disposition half-life is  $7.3 (\pm 4.0)$  hours. Inter-subject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

The extent of absorption of etodolac is not affected when etodolac is administered after a meal, but the  $C_{\text{max}}$  is reduced by 50% and  $T_{\text{max}}$  increased by 1.4-3.8 hours.

Etodolac is currently marketed as Lodine<sup>R</sup> manufactured by Wyeth-Ayerst Laboratories and is available as 200 and 300 mg capsules and 400 mg tablets. Lodine<sup>R</sup> is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis, and also for the management of pain. The recommended dose for acute pain is 200-400 mg every 6-8 hours as needed, not to exceed a total daily dose of 20 mg/kg body weight. The recommended dose for osteoarthritis is initially 800 to 1200 mg/day in divided doses, followed by dosage adjustment within the range of 600 to 1200 mg/day given in divided doses. The total daily dose of Lodine<sup>R</sup> should not exceed 1200 mg. For patients weighing 60 kg or less, the total daily dose should not exceed 20 mg/kg.

## **II. STUDY #1. TWO-WAY CROSSOVER FASTING STUDY**

### **A. Protocol #P95-297**

The objective of this study is to compare the bioavailability of the sponsor's etodolac 400 mg tablet and that of Lodine<sup>R</sup> 400 mg tablet, marketed by Wyeth-Ayerst in fasting volunteers.

**Study Site and Principal Investigator:** The clinical portion of the study was conducted at \_\_\_\_\_ as co-principal investigators, during 12/10/96 - 12/18/96. The analytical portion of the study was conducted at the facility of \_\_\_\_\_ during 1/9/96-1/18/96.

**Study Design:** The study was conducted in a randomized, 2-treatment, 2-period, single dose crossover design. The study protocol dated 9/27/95 and informed consent form were approved by \_\_\_\_\_ on 01/19/96.

A total of twenty-six healthy men were recruited and 26 completed the study. Volunteer \_\_\_\_\_ was initially dosed as subject #16. However, secondary to difficulty in phlebotomy and protocol blood collection schedule, the investigators elected to terminate study participation of Subject \_\_\_\_\_ at 0.33 hour, period I. At that time a new volunteer, \_\_\_\_\_ was recruited as subject #16, and completed the study as indicated in the protocol.

### **Volunteer Selection**

- The subjects were 18-45 years old males and all weighed within 10% of their ideal body weight.
- Subjects were screened within 21 days prior to study Period I dosing for sound health including general observation, demographics, medical and medication history, physical examination, blood pressure, heart rate, temperature check, EKG, and clinical laboratory procedures (hematology, clinical chemistry, HIV 1 & 2 antibody and hepatitis B surface antigen screens, urinalysis, and urine drug screen).
- Exit procedures included a physical examination, blood pressure, heart rate, temperature, and clinical laboratory (hematology, clinical chemistry) within 14 days after the last blood sample collection.

**Exclusion Criteria:** Exclude volunteers with/who

- Recent history of drug or alcohol abuse.
- Presence of clinically significant disorder involving cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s), or psychiatric disease.
- Clinical lab. results significantly outside the accepted values.

- Positive hepatitis B surface antigen or HIV 1 & 2 antibody.
- History of clinically significant allergies.
- Clinically significant illness within 4 weeks prior to the study.
- Currently use tobacco.
- Used drugs, which induce hepatic drug metabolism, within 30 days prior to the study.
- Positive urine drug screen.
- Donated 150 mL blood within 30 days prior to the study.
- Donated plasma within 14 days prior to the study.
- Received investigational drugs within 30 days prior to the study.
- Used prescription drugs within 14 days prior to the study.

**Restrictions:** The volunteers were instructed as follows:

- No nonprescription drugs within 7 days prior to the study.
- No concomitant medication during the study.
- Abstain from consuming caffeine and/or xanthine-containing food or drink, at least 48 hours prior to and during blood collection period.
- Abstain from consuming alcohol, at least 48 hours prior to and during blood collection period.

#### **Treatment**

**A -Test Drug:** Etodolac tablet, 1 x 400 mg, Invamed, Inc., Lot # D951001  
potency 98.4%. Batch Size:

**B -Reference Drug:** Lodine<sup>R</sup> tablet, 1 x 400 mg, Wyeth-Ayerst Laboratories, Lot #9951053, potency 99.8%, expires 8/97.

**Fluid and Food Intake:** Each treatment was taken with 240 mL of water at room temperature, which was not permitted during the one hour pre-dose and two hours post-dose period. At two hours post-dose all subjects consumed 240 mL of water. Four hours post-dose, water was allowed *ad libitum*. All subjects fasted for 10 hours prior to dosing and until 4 hours post-dosing. Standard meals were provided as scheduled.

**Blood sampling:** 10 mL blood samples were collected in Vacutainers containing EDTA at 0 (pre-dose) 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, and 36 hours post-dosing. Plasma samples were prepared immediately and stored at -20°C until ready for analysis.

**Washout Period:** 7 Days between doses.

**B. Assay Methodology: Single-Dose, Fasting, 2-Way Crossover Study**

## C. Results

### 1. Pharmacokinetic Parameters

- The 90% CI for LAUCs and  $LC_{max}$  are within 80-125% as required (Table 1).
- Individual Test/Reference ratios for  $AUC_{0-t}$  ranged between with an average of 1.03 and CV of 13%.
- Individual Test/Reference ratios for  $AUC_{0-inf}$  ranged between with an average of 1.03 and CV of 14%.

- Individual Test/Reference ratios for  $C_{max}$  ranged between with an average of 1.00 and CV of 37%.
- Individual Test/Reference ratios for  $T_{max}$  ranged between with an average of 1.32 and CV of 78%.
- The ratios of  $AUC_{0-t}/AUC_{0-inf}$  ranged between with an average of 0.95 and CV of 3%.
- Individual PK parameters and summary data are given in Attachment-1.

**Table 1. Pharmacokinetic Parameters (%CV)**

Parameter	Test	Reference	Ratio, T/R	90% CI
$AUC_{0-T}$ , $\mu\text{g.Hr/mL}$	144.76 (27)	141.62 (26)	1.02	97.6-106.8
$AUC_{0-inf}$ , $\mu\text{g.Hr/mL}$	151.85 (28)	148.26 (26)	1.02	97.5-107.3
$C_{max}$ , $\mu\text{g/mL}$	25.46 (26)	26.82 (23)	0.95	84.8-105.1
$LAUC_{0-t}$ , $\mu\text{g.Hr/mL}$	139.33 (0.2)	136.77 (0.2)	1.02	97.6-106.3
$LAUC_{0-inf}$ , $\mu\text{g.Hr/mL}$	145.97 (0.2)	143.42 (0.2)	1.02	97.3-106.5
$LC_{max}$ , $\mu\text{g/mL}$	24.57 (1.1)	26.08 (1.0)	0.94	84.3-105.4
$T_{max}$ , Hr	2.1 (47)	2.12 (59)	0.99	
$T_{1/2}$ , Hr	7.56 (22)	7.51 (18)	1.01	
$K_{el}$ , $\text{Hr}^{-1}$	0.10 (20)	0.1 (20)	1.00	

**2. Blood/Plasma Drug Concentration:** The plasma concentration data are given in Table 2 and the data are plotted in Figure P-1 (Attachment-2).

TABLE 2. MEAN PLASMA ETODOLAC LEVELS FOR TEST AND REFERENCE PRODUCTS  
(UNIT: PLASMA LEVEL=MCG/ML TIME=HRS)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	4.96	5.03	5.27	7.24	0.94
0.67	12.91	10.50	14.86	10.30	0.87
1	14.98	10.89	16.81	9.48	0.89
1.33	15.98	10.31	16.67	8.51	0.96
1.67	16.44	8.56	17.67	8.53	0.93
2	17.78	7.66	18.04	7.08	0.99
2.5	17.76	6.57	17.93	6.03	0.99
3	18.00	5.44	17.40	6.83	1.03
4	14.83	4.40	14.00	5.50	1.06
6	7.23	2.42	6.72	2.53	1.08
8	5.13	1.72	4.96	1.89	1.04
10	4.12	1.44	3.86	1.51	1.07
12	3.47	1.21	3.52	1.90	0.99
16	2.48	1.11	2.32	0.95	1.07
24	1.19	0.68	1.10	0.66	1.08
30	0.65	0.49	0.62	0.49	1.05
36	0.40	0.41	0.35	0.37	1.13

1 = Test, 2 = Reference

**D. Adverse Effects: See Table below.**

Sign/Symptom	Test	Reference	Drug Related
Headache	3	0	Possible, remote and/or unrelated

The BE fasting study is acceptable.

**III. STUDY #2. THREE-WAY CROSSOVER LIMITED FOOD STUDY**

**A. Protocol # P95-298**

The study site, investigators, subject selection criteria, drug products, blood sampling schedule, analytical assay, methods validation, etc. were same as in the fasting study. Certain protocol differences are indicated below.

**Subjects:** 18 Healthy male volunteers participated in the study, but subject #7 dropped out prior to Period II dosing, and 17 subjects completed the study

**Study Design:** Randomized, 3-Way crossover, 3-period, 6-sequence study.

**Drug Regimen**

- A. Invamed Etodolac 400 mg tablets administered under fasting conditions.
- B. Invamed Etodolac 400 mg tablets administered under fed conditions.
- C. Wyeth-Ayerst's Lodine<sup>R</sup> 400 mg tablets administered under fed conditions.

**Dose:** Single Oral dose, etodolac 400 mg, administered with 240 mL water.

**Fasting/Food:** Regimen A: Subjects will be required to fast overnight before dosing and until 4 hours post-dosing.  
Regimen B & C: Subject will be required to fast overnight until 30 minutes prior to their dosing time, when they will be given standard breakfast. Standard meals will be provided at 4 hours post-dosing to all subjects.

**Water:** Water will be allowed *ad libitum* except during 1 hours predosing and 4 hours post-dosing period.

**Washout Period:** 7 Days between dosing.

## B. Results

### 1. Blood/Plasma Drug Concentration

The average plasma concentration data, test/reference ratios, and plasma profiles are given in Table 3, Table 4, and Figure P-2 (Attachment-3), respectively.

### 2. Pharmacokinetic Parameters

- Average pharmacokinetic parameters are given in Tables 5-8.
- The ratios of average test/reference (food) for AUCs and  $C_{max}$  are within 0.8-1.2 as required (Tables 6).
- ANOVA analysis showed no significant period effect on  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $T_{max}$ ,  $LAUC_{0-t}$ ,  $LAUC_{0-inf}$ , and  $LC_{max}$ .
- Individual PK parameters are given in Attachments 4-6.
- Food appears to decrease the  $C_{max}$  and AUCs of test product and increase  $T_{max}$ .

TABLE 3. MEAN PLASMA ETODOLAC LEVELS FOR TEST AND REFERENCE PRODUCTS

UNIT: PLASMA LEVEL=MCG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	5.43	6.60	0.55	1.29	2.31	3.27
0.67	16.72	11.74	3.94	6.51	9.45	11.98
1	18.91	9.35	6.67	7.02	12.21	8.96
1.33	19.70	7.32	9.73	6.80	14.94	6.62
1.67	19.34	5.05	11.85	7.25	16.08	4.86
2	19.02	5.25	12.97	7.43	15.98	3.58
2.5	17.67	4.76	12.04	5.25	14.63	2.92
3	15.46	4.12	12.13	3.95	12.72	2.29
4	13.10	3.77	11.80	3.48	11.39	2.30
6	6.31	2.03	8.98	3.12	7.32	1.83
8	4.31	1.39	5.16	2.01	4.39	1.25
10	3.31	1.02	3.88	1.56	3.23	0.89
12	2.71	0.91	3.31	1.47	2.80	0.86
16	1.68	0.56	1.89	0.72	1.77	0.68
24	0.91	0.44	0.89	0.50	0.90	0.40
30	0.40	0.35	0.43	0.33	0.39	0.24
36	0.18	0.20	0.20	0.20	0.19	0.21

1=Test Fasting, 2=Test Fed, 3=Reference Fed

TABLE 4. RATIO OF MEAN PLASMA ETODOLAC LEVELS FOR TEST AND REFERENCE PRODUCTS

UNIT: PLASMA LEVEL=MCG/ML TIME=HRS

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
0.33	9.80	2.35	0.24
0.67	4.24	1.77	0.42
1	2.83	1.55	0.55
1.33	2.02	1.32	0.65
1.67	1.63	1.20	0.74
2	1.47	1.19	0.81
2.5	1.47	1.21	0.82
3	1.27	1.22	0.95
4	1.11	1.15	1.04
6	0.70	0.86	1.23
8	0.84	0.98	1.18
10	0.85	1.02	1.20
12	0.82	0.97	1.18
16	0.88	0.94	1.07
24	1.02	1.02	1.00
30	0.92	1.03	1.12
36	0.91	0.98	1.08

TABLE 5. TEST MEAN/REFERENCE MEAN (ANTILOG CONVERSION)

UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	133.70	31.32	119.51	27.30	120.37	23.94
AUCT	129.29	31.34	114.98	27.17	116.31	23.64
CMAX	26.16	6.60	18.13	4.97	21.74	6.39
KE	0.10	0.02	0.11	0.02	0.10	0.02
LAUCI	129.98	0.25	116.33	0.25	118.04	0.21
LAUCT	125.44	0.26	111.68	0.26	113.95	0.21
LCMAX	25.38	0.26	17.44	0.29	21.00	0.26
THALF	7.04	1.04	6.74	1.27	6.95	1.17
TMAX	1.52	0.84	3.06	1.91	1.49	0.59

1=Test Fasting, 2=Test Fed, 3=Reference Fed

TABLE 6. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION)

UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.12	1.11	0.99
AUCT	1.12	1.11	0.99
CMAX	1.44	1.20	0.83
KE	0.94	0.98	1.04
LAUCI	1.12	1.10	0.99
LAUCT	1.12	1.10	0.98
LCMAX	1.46	1.21	0.83
THALF	1.05	1.01	0.97
TMAX	0.50	1.02	2.05

1=Test Fasting, 2=Test Fed, 3=Reference Fed

TABLE 7. LSMEANS AND 90% CONFIDENCE INTERVALS

UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR

	LSMEAN1	LSMEAN2	LSMEAN3	LOWCI12	UPPCI12	LOWCI13
PARAMETER						
AUCI	132.08	117.90	118.87	108.47	115.57	107.60
AUCT	127.71	113.41	114.80	108.77	116.46	107.45
CMAX	25.88	17.89	21.31	127.60	161.62	107.15
LAUCI	128.08	114.60	116.40	108.28	115.34	106.61
LAUCT	123.57	109.98	112.30	108.56	116.28	106.32
LCMAX	25.05	17.26	20.58	127.53	165.09	106.96

1=Test Fasting, 2=Test Fed, 3=Reference Fed

TABLE 8. LSMEANS AND 90% CONFIDENCE INTERVALS

UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR

	UPPCI13	LOWCI23	UPPCI23
PARAMETER			
AUCI	114.64	95.67	102.71
AUCT	115.05	94.99	102.59
CMAX	135.73	69.69	98.26
LAUCI	113.56	95.40	101.61
LAUCT	113.88	94.63	101.36
LCMAX	138.47	73.72	95.43

1=Test Fasting, 2=Test Fed, 3=Reference Fed

### C. Adverse Effects

No significant differences between test and references were observed (See the table below).

Sign/Symptom	Test Fast	Test Fed	Reference Fed	Drug Related
Headache	0	2	4	Possible/Probable
Abdominal Pain	1	0	0	Possible/Probable
Dry Mouth	1	0	0	Possible/Probable

The limited food study is acceptable

### III. *IN VITRO* RESULTS (DISSOLUTION): See Table below.

**TABLE 9. *In Vitro* Dissolution Testing**

#### A. Conditions

Method, Apparatus I (Basket)    RPM: 100    No. of Units: 12  
Medium: Potassium Phosphate Buffer, 0.05M at pH 7.5    Volume: 1000 mL  
Reference Drug: Lodine<sup>®</sup> 400 mg Tablets    Manufacturer: Wyeth-Ayerst  
Assay Methodology:

#### B. Results

Sampling Time	Test Product			Reference Product		
(Minutes)	Mean % Dissol	Range	CY	Mean % Dissol	Range	CY
	Lot D951001		Strength 400 mg	Lot # 9951053		
5	22.7		17.8	17.3		27.6
10	63.1		6.9	56.8		10.5
20	100.0		1.2	98.8		2.4
30	100.4		0.8	100.1		1.0

The dissolution data is acceptable.

### IV. COMPOSITION

All ingredients are within the IIG, 1996 limits, except \_\_\_\_\_, which is color coating agent and is not listed in the IIG.

[Not for Release under F.O.I.]

TABLE 10. Comparison of Test and Reference Products (Amounts in mg/Tablet)

Ingredients	Test Formulation	Reference Formulation
Etodolac (Micronized)	400	400
Microcrystalline Cellulose, NF		
Lactose Monohydrate, NF		
Povidone, USP		----
Sodium Starch Glycolate, NF		
Magnesium Stearate, NF		
Yellow *		
Purified Water <sup>3</sup>		
Cellulose		
Gelatin		
Iron Oxide		
Sodium Lauryl Sulfate		
Titanium Dioxide		
Talc		
Total	700	—

---

<sup>2</sup> Not listed in IIG, 1996.

<sup>3</sup> Water is used during the manufacturing process and not in the finished product.

## V. DEFICIENCY

None.

## VI. RECOMMENDATION

1. The fasting and the non-fasting bioequivalence studies conducted by Invamed, Inc. on its Etodolac 400 mg tablet, Lot #D951001, comparing it to Lodine<sup>R</sup> 400 mg tablet, Lot #9951053, manufactured by Wyeth-Ayerst Laboratories, Inc. have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Invamed's etodolac 400 mg tablets, are bioequivalent to the Lodine<sup>R</sup> 400 mg tablets manufactured by Wyeth-Ayerst.
2. The dissolution tests conducted by Invamed, Inc. on its Etodolac 400 mg tablet, Lot #D951001, comparing to Lodine<sup>R</sup> 400 mg tablet Lot #9951053, manufactured by Wyeth-Ayerst have been found acceptable by the Division of Bioequivalence.

The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.5 at 37° using USP 23 Apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

Not less than \_\_\_\_\_ of the labeled amount of etodolac in the dosage form is dissolved in 30 minutes.

The above recommendations should be forwarded to the sponsor.

S. P. Shrivastava, Ph.D.  
Division of Bioequivalence  
Review Branch II

RD INITIALED S Nerurkar  
FT INITIALED S Nerurkar

Date 7/18/96

Concur: \_\_\_\_\_ Date: 7/29/96

Keith K. Chan, Ph.D.  
Director  
Division of Bioequivalence

Attachment - 1

ETODOLAC 400 MG TABLET FASTING STUDY  
INVAMED P95-297  
PK PARAMETER VALUES BY PRODUCT AND SUBJECT

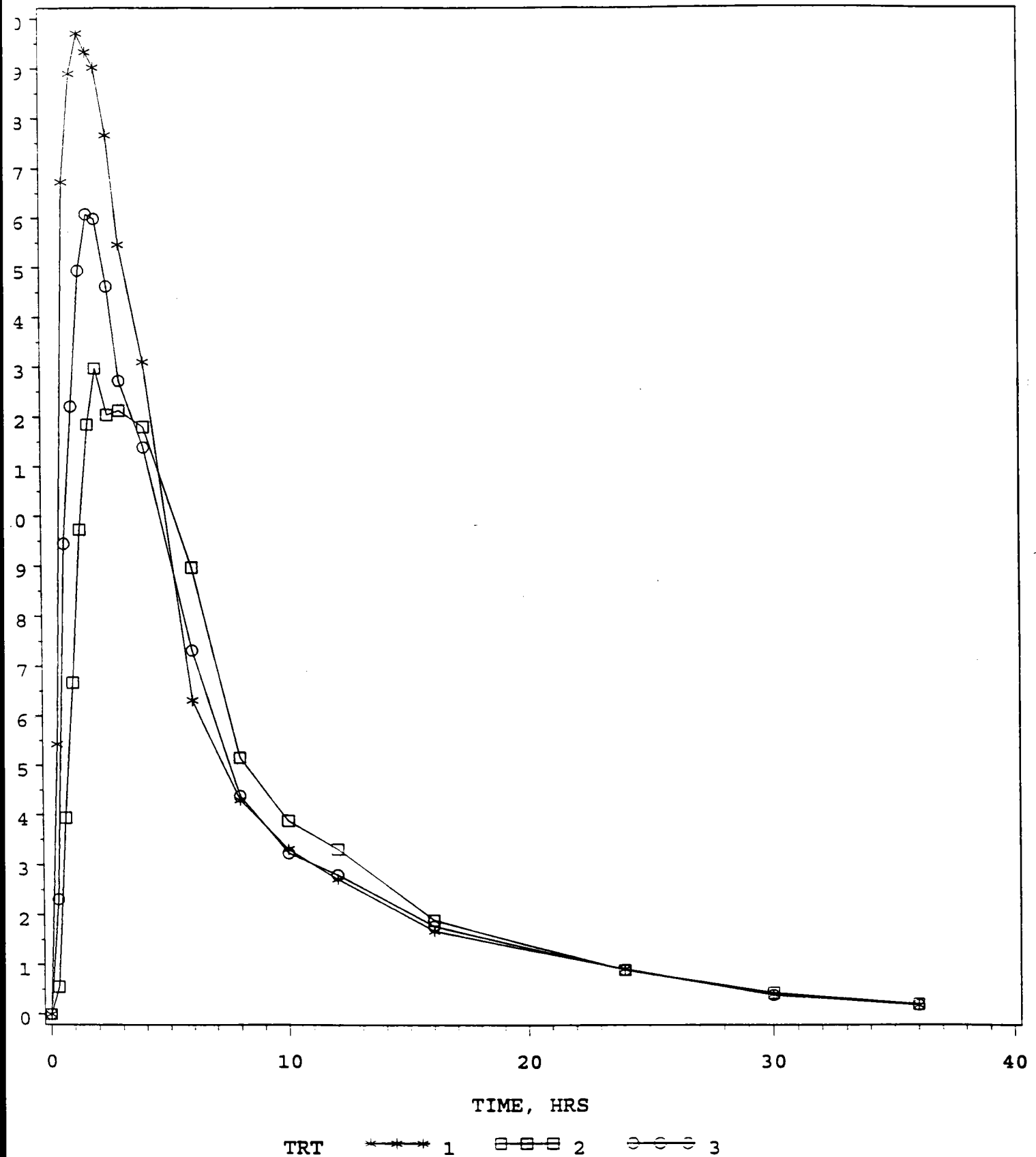
----- PRODUCT=A:TEST -----											
SUBJECT	PERIOD	SEQUENCE	AUCTLQC	AUCINF	C <sub>MAX</sub>	T <sub>MAX</sub>	KELM	THALF	LAUCTLQC	LAUCINF	LC <sub>MAX</sub>
1	1	1	118.29	121.58	30.2	1.00	0.1248	5.55	4.77313	4.80059	3.40784
2	1	1	189.31	198.83	44.0	0.67	0.0752	9.22	5.24338	5.29247	3.78419
3	2	2	136.44	140.21	29.3	1.33	0.0890	7.79	4.91590	4.94312	3.37759
4	1	1	152.73	157.90	27.2	1.67	0.1051	6.59	5.02869	5.06196	3.30322
5	2	2	205.93	222.54	28.1	3.00	0.0735	9.43	5.32755	5.40509	3.33577
6	2	2	202.82	212.90	34.4	2.50	0.0865	8.01	5.31230	5.36084	3.53806
7	2	2	135.47	139.52	18.1	3.00	0.1064	6.52	4.90874	4.93821	2.89591
8	1	1	231.41	241.92	36.3	1.33	0.0796	8.71	5.44418	5.48862	3.59182
9	1	1	169.03	176.16	25.1	2.50	0.0890	7.79	5.13009	5.17138	3.22287
10	1	1	128.46	133.57	26.4	2.00	0.0849	8.16	4.85564	4.89465	3.27336
11	1	1	76.63	82.50	25.9	0.67	0.1364	5.08	4.33903	4.41279	3.25424
12	2	2	116.56	119.97	22.1	1.67	0.1117	6.20	4.75843	4.78727	3.09558
13	2	2	159.89	166.88	20.5	3.00	0.0841	8.24	5.07451	5.11729	3.02042
14	2	2	74.93	78.52	16.8	3.00	0.1204	5.76	4.31652	4.36342	2.82138
15	1	1	188.96	203.85	22.5	2.00	0.0678	10.22	5.24153	5.31741	3.11352
16	1	1	161.77	165.78	32.6	1.33	0.1095	6.33	5.08615	5.11064	3.48431
17	1	1	141.03	144.69	26.2	3.00	0.0950	7.30	4.94901	4.97458	3.26576
18	2	2	152.66	174.22	13.7	4.00	0.0589	11.77	5.02822	5.16030	2.61740
19	1	1	139.63	144.70	24.8	1.33	0.1018	6.81	4.93901	4.97466	3.21084
20	2	2	79.80	82.74	17.1	2.50	0.1213	5.72	4.37949	4.41572	2.83908
21	2	2	164.39	168.98	23.6	3.00	0.1154	6.00	5.10225	5.12980	3.16125
22	2	2	112.20	115.48	21.1	2.00	0.1155	6.00	4.72030	4.74912	3.04927
23	2	2	123.34	129.08	18.1	4.00	0.0795	8.72	4.81493	4.86039	2.89591
24	1	1	119.26	127.08	20.3	2.55	0.1039	6.67	4.78134	4.84484	3.01062
25	1	1	123.30	128.91	22.3	0.67	0.0834	8.31	4.81462	4.85912	3.10459
26	2	2	159.56	169.63	35.3	1.00	0.0709	9.77	5.07243	5.13360	3.56388

ETODOLAC 400 MG TABLET FASTING STUDY  
INVAMED P95-297  
PK PARAMETER VALUES BY PRODUCT AND SUBJECT

----- PRODUCT=B:REFERENCE -----											
SUBJECT	PERIOD	SEQUENCE	AUCTLQC	AUCINF	C <sub>MAX</sub>	T <sub>MAX</sub>	KELM	THALF	LAUCTLQC	LAUCINF	LC <sub>MAX</sub>
1	2	1	98.89	102.67	39.0	0.67	0.1122	6.18	4.59404	4.63153	3.66356
2	2	1	170.51	176.11	35.2	1.67	0.0894	7.75	5.13881	5.17108	3.56105
3	1	2	108.18	111.85	19.1	2.50	0.1014	6.83	4.68376	4.71720	2.94969
4	2	1	142.74	146.89	28.5	2.00	0.1131	6.13	4.96103	4.98966	3.34990
5	1	2	148.89	156.40	12.7	6.00	0.0919	7.54	5.00318	5.05245	2.54160
6	1	2	223.58	236.74	28.9	4.00	0.0805	8.61	5.40977	5.46696	3.36384
7	1	2	154.33	159.61	30.6	1.67	0.0886	7.82	5.03909	5.07273	3.42100
8	2	1	199.04	203.40	27.9	3.00	0.0947	7.32	5.29349	5.31516	3.32863
9	2	1	162.62	172.31	28.1	2.50	0.0819	8.46	5.09139	5.14929	3.33577
10	2	1	160.62	167.92	27.2	2.00	0.0820	8.45	5.07901	5.12347	3.30322
11	2	1	80.21	88.04	20.7	2.50	0.1314	5.27	4.38460	4.47783	3.03013
12	1	2	126.59	130.46	31.7	1.00	0.1063	6.52	4.84097	4.87105	3.45632
13	1	2	151.04	157.38	23.4	2.00	0.0806	8.60	5.01756	5.05869	3.15274
14	1	2	84.49	88.76	19.7	1.00	0.1122	6.18	4.43662	4.48593	2.98062
15	2	1	193.17	210.60	28.5	0.67	0.0654	10.60	5.26356	5.34995	3.34990
16	2	1	173.30	177.10	40.2	1.33	0.1121	6.18	5.15500	5.17669	3.69387
17	2	1	151.59	155.49	33.3	3.00	0.0944	7.34	5.02117	5.04657	3.50556
18	1	2	165.54	181.80	23.9	4.00	0.0640	10.84	5.10921	5.20290	3.17388
19	2	1	117.74	120.95	21.1	1.00	0.0939	7.38	4.76852	4.79537	3.04927
20	1	2	78.13	91.25	22.6	1.67	0.0884	7.84	4.35836	4.51356	3.11795
21	1	2	157.99	160.75	29.3	3.00	0.1140	6.08	5.06250	5.07984	3.37759
22	1	2	115.57	118.80	24.1	3.00	0.1154	6.00	4.74991	4.77741	3.18221
23	1	2	136.89	140.88	31.8	1.00	0.0918	7.55	4.91918	4.94789	3.45947
24	2	1	109.17	116.25	23.4	0.67	0.1019	6.80	4.69289	4.75572	3.15274
25	2	1	117.32	121.19	24.8	1.33	0.0875	7.92	4.76494	4.79734	3.21084
26	1	2	153.89	161.25	21.7	2.00	0.0775	8.95	5.03623	5.08294	3.07731

# FIG P-2. PLASMA ETODOLAC LEVELS

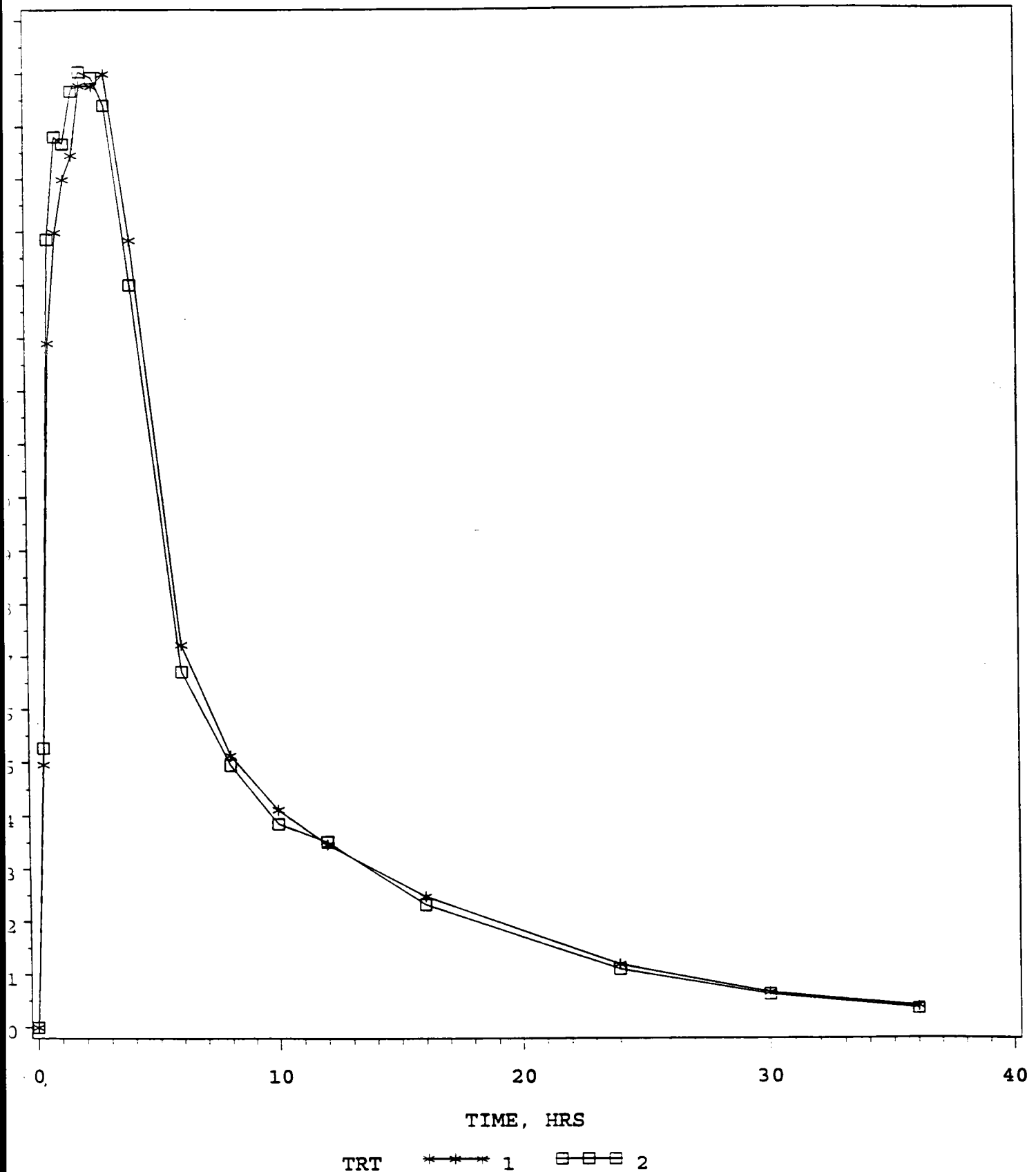
ETODOLAC TABLETS, 400 MG, ANDA #74-846  
UNDER NON-FASTING CONDITIONS  
DOSE=400 MG



1=TEST-FASTING (INVAMED) 2=TEST-FED (INVAMED) 3=REFERENCE-FED (WYETH-AYERST)

## FIG P-1. PLASMA ETODOLAC LEVELS

ETODOLAC TABLETS, 400 MG, ANDA #74-846  
UNDER FASTING CONDITIONS  
DOSE=1 X 400 MG



1=TEST PRODUCT (INVAMED)    2=REFERENCE PRODUCT (WYETH-AYERST)

Attachment - 4

ETODOLAC 400 MG TABLET FOOD STUDY  
INVAMED P95-298  
PK PARAMETERS

----- PRODUCT=A:TEST FAST -----								
SUBJECT	AUCTLQC	AUCINF	C <sub>MAX</sub>	T <sub>MAX</sub>	KELN	T <sub>HALF</sub>	REGSTART	REGENO
1	157.7	163.3	39.4	0.67	0.0862	8.04	8	36
2	82.1	85.9	17.6	2.00	0.1133	6.12	8	24
3	132.5	137.8	31.3	2.00	0.0907	7.64	10	30
4	162.5	166.3	30.9	1.33	0.0934	7.42	8	36
5	134.0	137.4	35.3	1.00	0.1108	6.26	8	30
6	138.6	141.6	22.7	1.67	0.1160	5.98	8	30
8	141.4	144.9	26.4	1.33	0.0920	7.54	10	36
9	107.6	116.3	19.3	2.00	0.0740	9.37	8	30
10	176.2	181.1	28.7	2.50	0.0936	7.41	6	36
11	111.5	114.5	20.1	4.00	0.1407	4.93	6	24
12	183.5	188.0	29.8	1.33	0.0902	7.69	8	36
13	142.0	145.8	25.9	1.33	0.0917	7.56	8	36
14	94.4	99.7	27.7	1.00	0.1021	6.79	8	24
15	136.4	139.5	21.5	0.67	0.1092	6.35	6	36
16	115.1	119.7	17.4	0.67	0.0881	7.87	6	36
17	70.5	73.8	18.4	1.67	0.1147	6.04	8	24
18	111.9	117.3	32.4	0.67	0.1035	6.69	8	24

001228

ETODOLAC 400 MG TABLET FOOD STUDY  
INVAMED P95-298  
PK PARAMETERS

----- PRODUCT=B:TEST FED -----								
SUBJECT	AUCTLQC	AUCINF	C <sub>MAX</sub>	T <sub>MAX</sub>	KELM	T <sub>HALF</sub>	REGSTART	REGENO
1	138.6	142.6	25.40	1.67	0.0943	7.35	10	36
2	75.7	77.8	9.38	6.00	0.1587	4.37	8	24
3	130.6	133.9	22.20	2.00	0.0922	7.52	10	36
4	143.7	148.3	21.30	2.50	0.0936	7.40	8	36
5	120.5	125.5	15.30	3.00	0.1083	6.40	8	30
6	132.4	135.9	16.00	4.00	0.0972	7.13	8	36
8	114.3	118.4	10.50	6.00	0.1021	6.79	10	36
9	106.3	110.7	20.30	1.33	0.0916	7.57	8	30
10	163.1	167.5	15.00	6.00	0.1038	6.68	8 ✓	36
11	100.5	107.9	21.40	1.33	0.1512	4.58	8	16
12	148.2	153.3	20.30	4.00	0.0922	7.52	8	36
13	123.2	132.6	25.80	2.00	0.0808	8.58	8	30
14	83.3	87.5	16.60	2.00	0.0758	9.15	8	36
15	114.1	116.8	13.70	6.00	0.1173	5.91	10	36
16	110.1	113.4	15.30	2.50	0.1130	6.13	8	30
17	62.5	68.5	15.20	1.00	0.1267	5.47	8	16
18	87.6	91.1	24.50	0.67	0.1158	5.98	8	24

Attachment-6

ETODOLAC 400 MG TABLET FOOD STUDY  
INVAMED P95-298  
PK PARAMETERS

----- PRODUCT=C:REFERENCE FED -----

SUBJECT	AUCTLQC	AUCINF	C <sub>MAX</sub>	T <sub>MAX</sub>	KELM	T <sub>HALF</sub>	REGSTART	REGENO
1	145.2	149.7	21.5	1.33	0.0904	7.67	10	36.0
2	81.7	84.6	17.1	2.00	0.1326	5.23	8	24.0
3	114.3	118.9	16.0	0.67	0.1005	6.89	10	30.0
4	130.9	134.1	20.4	1.67	0.0949	7.30	8	36.0
5	109.7	113.1	22.9	1.33	0.1090	6.36	8	30.0
6	138.9	142.8	40.0	0.67	0.1058	6.55	8	30.0
8	112.2	117.7	21.8	1.33	0.0758	9.15	12	36.0
9	106.8	112.4	19.7	1.00	0.0772	8.98	8	36.0
10	156.2	160.3	17.7	2.50	0.1035	6.69	12	36.0
11	107.6	110.3	30.9	1.00	0.1479	4.69	4	24.0
12	149.9	155.6	18.7	1.33	0.0920	7.53	6	36.0
13	128.4	132.4	23.2	2.00	0.0916	7.57	8	34.9
14	83.9	88.2	18.2	2.00	0.0879	7.89	8	30.0
15	119.2	123.2	21.6	1.67	0.1058	6.55	10	30.0
16	119.5	122.6	18.4	2.50	0.1004	6.90	8	36.0
17	75.6	78.7	13.0	1.67	0.1213	5.72	8	24.0
18	97.2	101.7	28.5	0.67	0.1076	6.44	8	24.0

001230

# OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-846

DRUG & DOSAGE FORM : Etodolac Tablets, 400 mg

STRENGTH (s) :

TYPE OF STUDY:

STUDY SITE: CLINICAL

(SD)

(SDF)

MULT

ANALYTICAL :

SPONSOR :

INVAMED

OTHER Dissolution.

STUDY SUMMARY : Passes both fasting and nonfasting studies.

Parameter	test	ref	ratio	90% CI (log).
C <sub>max</sub> (ng/ml)	25.5	26.8	0.95	84.8-105.1
AUC(0-T) $\mu$ g $\cdot$ hr/ml	144.8	141.6	1.02	97.6-106.8
AUC(0-Inf) $\mu$ g $\cdot$ hr/ml	151.9	148.3	1.02	97.5-107.3
T <sub>max</sub> hr	2.1	2.1	0.99	—
Half-life hr	7.6	7.5	1.01	—

## DISSOLUTION :

Conditions

Time(min)

Test Mean(range)

Ref. Mean(range)

15 10

63.1

56.8

30 20

100.0

98.8

45 30

100.4

100.1

Q =

10 in 30 min.

PRIMARY REVIEWER : S. f. Shrivastava

BRANCH : II

INITIAL : \_\_\_\_\_

DATE : 7/19/96

BRANCH CHIEF : S. G. NERURKAR

BRANCH :

INITIAL : \_\_\_\_\_

DATE : 7/26/1996

DIRECTOR  
DIVISION OF BIOEQUIVALENCE

INITIAL : \_\_\_\_\_

DATE : 7/29/96

DIRECTOR  
OFFICE OF GENERIC DRUGS

INITIAL : N/A

DATE : \_\_\_\_\_

# DBE STUDY APPROVAL FORM

ANDA#: 74-846

DRUG/FORM(S)/STRENGTH: Etodolac

RLD (FIRM): Wyeth-Ayerst

TYPE OF STUDY: (SD) (SD/fed)

Therapeutic Category/Dosage Regimen:

Biopharm classification (solubility/permeability):

First Generic (Y/N): N

FIRM: Invamed

Tablets, 400 mg

BIO-REVIEWER: S. P. Shrivastava

MD

Others: Dissolution

## Clinical Procedure - Center

# of subjects (planned+extra): 26

# of subjects completed: 26

Subset analysis:

Randomization: ✓

Dose administration: ✓

Safety Summary: ✓

P study

Investigator:

# dropped out (reason): One sub #16 replaced  
# in data analysis (reason): within an hr. due to blood collection problems.

L→26

Demographic: ✓

Blood sample: ✓

## Analytical Procedure - Center

Analytical method:

Pre-study validation:

Stability: long (✓) / short (✓) / bench (✓) / freeze-thaw cycle (✓)

Within-study validation:

Calibration: 1S 0.3 - 40 µg/mL QC samples: 0.6 - 30 µg/mL

Comments:

CV's < 5%, Accuracy - OK, Recovery 98%

## PK/Statistical Analysis - Center

PK Calculation procedure: Std. Meets the 80-125% criteria for 90% CI

Mean plasma profile: Ratios - Good

Summary of PK parameters:

Comments:

Meets the food effect criteria also of being within 20% of the ref. for AUCs + Cmax.

Investigator:

Statistical calculation procedure: Std.

Comments (estimated intra-, inter- and total variabilities):

Intra - Aact - 9.6%

" Cmax 22%

Intra - Subject - 37%

" - Cmax - 26%

In Vitro Dissolution/USP specs:

Firm submitted data:

? Diss. in 30 min. P04 buffer 0.05M, pH 7.5.  
Meets the FDA requirements - Basket 100%  
@ 5, 10, 20, 30 min. ~20% in 5 min, ~60% in 10 min, 20-30 min > 90%.

Waiver Request

N/A

Comparison to Past Generic & Reference Products

file:Protocol/fdabiock.wp (version 8/23/95)

Approved 7/29/96